January 14, 2005

Cynthia Graham, Ph.D.
Product Safety & Regulatory Affairs
Bayer CropScience LP
100 Bayer Road, Building #5
Pittsburgh, PA 15205-9741

Dear Dr. Graham:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for carbonothioic dihydrazide posted on the ChemRTK HPV Challenge Program Web site on February 25, 2004. I commend Bayer CropScience LP for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Bayer CropScience advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Donald Rodier, Acting Chief of the HPV Chemicals Branch, at 202-564-7633. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Carbonothioic Dihydrazide

Summary of EPA Comments

The sponsor, Bayer CropScience LP, submitted a test plan and robust summaries to EPA for carbonothioic dihydrazide [thiocarbohydrazide (TCH); CAS No. 2231-57-4] dated December 29, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 25, 2004.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The submitter needs to provide a quantitative value for the water solubility endpoint.

2. Environmental Fate. The submitter needs to include a technical discussion in the robust summary about this chemical's hydrolysis potential and provide measured ready biodegradation data.

3. Health Effects. Submitted data are adequate for the acute toxicity and gene mutation endpoints for the purposes of the HPV Challenge Program. The submitter needs to address some critical data elements in robust summaries. EPA agrees that a developmental study is needed. The submitter sought an exemption from repeated-dose and reproductive toxicity testing via a closed-system intermediate claim; however, support for this claim was inadequate. Therefore, the submitter needs to conduct a combined screening test for repeated-dose/reproduction/developmental toxicity. In addition, in lieu of conducting the proposed *in vivo* mouse micronucleus assay, EPA encourages *in vitro* testing to address the chromosomal aberrations endpoint.

4. Ecological Effects. EPA agrees with the submitter's proposal to conduct testing on algae. The submitter also needs to conduct acute toxicity testing in fish and daphnia following OECD guidelines.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Carbonothioic Dihydrazide Challenge Submission

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The data provided by the submitter for melting point, boiling point, vapor pressure, and partition coefficient are adequate for the purposes of the HPV Challenge Program.

Water solubility. The submitter provided a qualitative statement indicating this chemical is "of very high solubility" which is not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured, quantitative data for this endpoint. EPA located a measured value of 5,500 mg/L at 24.7 °C from a literature source (Audrieth et al. 1954 J. Org. Chem., 19:733-740 {BEILSTEIN On-line}). The submitter may add this value to its robust summary.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The submitted data for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program.

Stability in water. The submitter needs to include a technical discussion of hydrolysis potential in the

robust summary and support its conclusion by including quantitative results of analytical monitoring during the aquatic toxicity testing, as suggested in the test plan. If loss of test chemical occurs, then the submitter needs to provide measured hydrolysis data following OECD guidelines.

Biodegradation. The submitter concludes from BIOWIN calculations that TCH is readily biodegradable. However, estimated biodegradation data are not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured ready biodegradation data following OECD TG 301.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The available data are adequate for the acute toxicity and gene mutation endpoints for the purposes of the HPV Challenge Program. The submitter needs to address some critical data elements in the robust summaries. The submitter has proposed to conduct an *in vivo* mouse micronucleus assay (OECD TG 474) and a developmental toxicity study (OECD TG 414). No data were provided for repeated-dose toxicity and reproductive toxicity because the submitter claimed this chemical as a closed system intermediate subject to reduced health effects testing.

Acute Toxicity. The submitter needs to address the following discrepancies in the test plan: (1) The test plan reports the test animals used in the acute dermal toxicity study as rabbits (p. 2 of 5) whereas Table 1 of the test plan (p. 4 of 5) and both robust summaries for acute dermal toxicity (p. 17-18/27) report test animals as rats; (2) Table 1 of the test plan (p. 4 of 5) needs to reflect the acute toxicity inhalation value as an "LC_{50}", not as an "LC."

Genetic Toxicity. Although the submitter proposed to conduct an *in vivo* micronucleus assay according to OECD Guideline 474 to satisfy the chromosomal aberration endpoint, EPA encourages conducting an *in vitro* genotoxicity study (OECD TG 473) rather than an *in vivo* study unless the properties of the chemical indicate otherwise.

Repeated-Dose, Reproductive and Developmental Toxicity. The submitter's plan to conduct testing according to OECD TG 414 would satisfy only the developmental toxicity endpoint. The submitter provided a separate, confidential business information-supported claim that the sponsored chemical is a closed-system intermediate and thus exempt from repeated-dose and reproductive toxicity testing. EPA has determined that the claim is not supported by the submitted information. Therefore, the submitter needs to provide data for repeated-dose and reproductive toxicity. EPA recommends a combined screening test according to OECD TG 422 to address the repeated-dose toxicity, reproductive toxicity, and developmental toxicity endpoints in lieu of a developmental toxicity study (OECD TG 414).

Ecological Effects (fish, invertebrates, and algae)

Although the submitter's plan to conduct an algal toxicity study of the sponsored substance according to OECD TG 201 is appropriate, the submitter's rationale for testing only in algae, based on the ECOSAR prediction that the sponsored substance is most toxic to algae, is inadequate. In the HPV Challenge program, complete SIDS-level testing in three species is necessary. Therefore, the submitter needs to conduct acute toxicity studies in fish (OECD Guideline 203) and daphnia (OECD Guideline 202) or provide data for these endpoints on a close analog.

The test plan reports the ECOSAR-predicted daphnia toxicity value as a 24-hour value (p. 2 of 5), whereas Table 1 of the test plan and the robust summary for acute daphnia toxicity report a 48-hour value. The submitter needs to address this discrepancy.

Specific Comments on the Robust Summaries

Health Effects

Acute Toxicity. The robust summary for the key study of acute inhalation toxicity was missing study details such as the guideline followed, the mean diameter of the dust particles, and the statistical methodology.

The two robust summaries submitted for acute dermal toxicity tests were missing study details such as the guideline followed and the number of animals/sex/concentration used.

Genetic Toxicity. The robust summary submitted for a *Salmonella* mutagenicity test was missing study details such as indication of the use of a negative control, positive control response, number of replicates per concentration, culture conditions, criteria for a positive response, and statistical methodology.

The robust summary submitted for a DNA damage and repair assay was missing study details such as culture conditions, specific dose response results, positive and negative control response, number of cells per culture counted for UDS (unscheduled DNA synthesis) determination, statistical methodology, method used to block entry of cells into S-phase, and reproducibility of positive response.

Ecological Effects

The submitter needs to provide the input values used for ECOSAR in the robust summaries for acute toxicity to fish, invertebrates, and toxicity to algae.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.